REMARKS

Claims 1 and 3-43 are pending. Of those claims, claims 3, 5, 9, 12-18, 21-22, 25-43 are withdrawn. Applicants have canceled claim 2 without prejudice or waiver of applicants' right to file for and obtain claims directed to any canceled subject matter in future divisional or continuing applications claiming priority from this application. Upon entry of this amendment, claims 1, 4, 6-8, 10, 11, 19, 20, 23 and 24 are under examination.

Applicants have amended claim 1 to specify that the cytokine-expressing cellular vaccine comprises proliferation-incompetent tumor cells that express GM-CSF. Support for this amendment is provided, for example, at specification page 4, lines 1; page 12, lines 13-22; page 15, lines 1-12; page 18, lines 10-11; page 20, lines 13-14 and lines 24-26; page 32, lines 1-4; and original claims 2 and 6.

Applicants have amended claims 4, 6-8, 11, 19, 23 and 24 to remove and correct the claim dependency from canceled claim 2.

None of the amendments introduces new matter.

THE REJECTIONS

35 U.S.C. § 112, first paragraph (enablement)
Claims 1, 2, 4, 6-8, 10, 11, 19, 20, 23, 24 and 26

The Examiner has rejected claims 1, 2 (canceled), 4, 6-8, 10, 11, 19, 20, 23, 24 and 26 (withdrawn) under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner contends that the specification does not provide a sufficient enabling description of a method for cancer therapy comprising administering a ***cellular vaccine*** in view of the Cancer Vaccine Fact Sheet from the National Cancer Institute (updated June

8, 2006). Specifically, the Examiner states that the Cancer Vaccine Fact Sheet states "that there are no licensed therapeutic vaccines to date" and concludes that it would take undue trial and error to practice the claimed invention. (Office Action, pp. 2-3).

Applicants have amended claim 1 (and claims dependent therefrom) to specify that the method for cancer therapy comprises administering a cytokine-expressing cellular vaccine comprising proliferation-incompetent tumor cells that express GM-CSF. The proliferation-incompetent tumor cells are administered in combination with at least one additional cancer therapeutic agent selected from a specific group of agents. Applicants respectfully submit that the specification provides adequate enablement for the claims as amended. The specification describes that vaccination of proliferation-incompetent (*e.g.*, by irradiation) tumor cells engineered to secrete GM-CSF stimulates potent, long-lasting and specific anti-tumor immunity that prevents tumor growth in a majority of mice challenged with non-transduced tumor cells (see, *e.g.*, p. 29, line 2 to p. 30, line 4; p. 31, lines 21-23; p. 39, line 28 to p. 40, lines 28-30; p. 40, lines 23-27). This is in contrast to the Examiner's contention that cellular vaccines would require undue experimentation.

The specification also describes that the combination of the cytokine-expressing cellular vaccine comprising proliferation-incompetent tumor cells that express GM-CSF and at least one additional cancer therapeutic agent is expected to increase the efficacy of anti-tumor protection. The specification describes several examples in which the combination of cellular vaccines comprising proliferation-incompetent tumor cells that express GM-CSF with cancer therapeutic agents results in enhanced therapeutic potency and efficacy relative to monotherapy (see, *e.g.*, Examples 1-8).

Based on these results, one of skill in the art would recognize that administering the specific combination of a cytokine-expressing cellular vaccine comprising proliferation-incompetent tumor cells that express GM-CSF with at least one additional cancer therapeutic agent selected from a specific group of agents, as recited in the amended claim, would result in enhanced therapeutic potency and/or efficacy relative to monotherapy. Thus, applicants respectfully submit that the present application provides sufficient enablement for one skilled in the art to make and use the invention without undue experimentation. Accordingly, applicants request that the Examiner withdraw the rejection.

35 U.S.C. § 112, first paragraph (written description)
Claim 1

The Examiner has rejected claim 1 under 35 U.S.C. § 112, first paragraph for lack of written description. The Examiner contends that applicants are not in possession of the term "cytokine-expressing cellular vaccine" because the specification discloses one example of a cytokine-expressing cellular vaccine, in particular, a vaccine expressing GM-CSF. The Examiner further contends that given the limited written description in the specification, the skilled artisan cannot envision all the contemplated structural possibilities of the cytokine-expressing cellular vaccine encompassed by the claims.

Applicants have amended claim 1 (and claims dependent therefrom) to specify that the cytokine-expressing cellular vaccine comprises proliferation-incompetent tumor cells that express GM-CSF, thereby obviating the Examiner's rejection. According, applicants request that the Examiner withdraw this rejection.

35 U.S.C. § 102(a)
Claims 1-2, 4, 6-7, 11, 19-20, 23-24 and 26

The Examiner has rejected claims 1, 2 (canceled), 4, 6-7, 11, 19-20, 23-24 and 26 (withdrawn) under 35 U.S.C. § 102(a) over Gri *et al.*, "OX40 ligand-transduced tumor cell vaccine synergizes with GM-CSF and requires CD40-Apc signaling to boost the host T cell antitumor response," *J. Immunol*, 170:99-106 (2003) ("*Gri*"). The Examiner states that *Gri* discloses a method of treating colon carcinoma by administering carcinoma cells transduced to express GM-CSF and OX40 ligand. The Examiner states that *Gri* teaches that OX40 ligand is functionally equivalent with anti-OX40 antibodies and concludes that a method of treating cancer by administering GM-CSF-expressing cells and anti-OX40 antibodies is inherent in the teachings of *Gri*. The Examiner further states that *Gri* further teaches that the GM-CSF-expressing cells are inactivated by irradiation and envisions using the method for human therapy.

Applicants respectfully traverse and submit that *Gri* fails to teach or suggest each and every limitation of the amended claims. In essence, the Examiner alleges that if OX-40 ligand can treat cancer when administered with GM-CSF-expressing cells (as suggested by *Gri*), then anti-OX40 antibodies must *necessarily* also treat cancer when administered with GM-CSF-expressing cells and, therefore, the claimed invention is inherently anticipated. But, for a reference to inherently anticipate, the unstated or implicit limitation or feature must "necessarily be present" when the reference is practiced or applied. In other words, the missing limitation must occur as a ***certainty***; the "mere *possibility*" that the reference may *sometimes* result in the limitation or characteristic is not enough. Here is how the Federal Circuit explained the inherency requirement in the well-known *Continental Can* case:

> Inherency, however, may not be established by probabilities or possibilities. **The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient**. If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught ***would result*** in the performance of the questioned function . . . the disclosure should be regarded as sufficient.
>
> *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) (emphasis added).

In *Continental Can*, of course, the Federal Circuit vacated the district court's finding of inherent anticipation and remanded the case so the court could get it right. *See Schering Corp. v. Geneva Pharms. Inc.*, 339 F.3d 1373, 1377-1378 (Fed. Cir. 2003) (setting forth the "necessary and inevitable" test of inherent anticipation); *see also SmithKline Beecham Corp. v. Apotex Corp.*, 74 U.S.P.Q.2d 1398, 1407 (Fed. Cir. 2005) (accepting inherent anticipation argument because producing PHC anhydrate according to the earlier reference "inevitably results" in production of at least some of the claimed PHC hemihydrate).

Applicants respectfully submit that the *Gri* disclosure does not ***necessarily and inevitably*** lead to treatment of cancer when anti-OX40 antibodies are administered with GM-CSF-expressing cells. *Gri* discloses that only 30% of mice injected with C26 colon carcinoma cells transduced with both the GM-CSF gene and the OX-40 ligand gene (C26/GM/OX40L) developed tumors and half of the mice showed subsequent tumor regression. *Gri* also discloses that the overall survival of mice injected with C26/GM/OX40L was 85% and that all mice rejected a subsequent challenge with live C26 cells, indicating the development of immunological memory. *Gri* also discloses that when the dose of C26/GM/OX40L cells was increased, the tumor grew in all mice and

regressed in a smaller number of cells, suggesting that tumor burden is a major obstacle to immune-mediated rejection.

The Examiner points to the last paragraph of *Gri* on page 105 as his support that OX40 ligand is functionally equivalent to anti-OX40 antibodies. The Examiner's analysis is incorrect. The last paragraph of *Gri* states, in part, that "[r]ecent adoptive immunotherapy experiments have shown that the coadministration of anti-OX40 Ab reduces the number of transferred T cells required to obtain remission of pulmonary metastasis and intracranial tumors" (citing Kjaergaard *et al.*, "Therapeutic Efficacy of OX-40 Receptor Antibody Depends on Tumor Immunogenicity and Anatomic Site of Tumor Growth," Cancer Research, 60:5514-5521 (2000) ("*Kjaergaard*"), a copy of which is submitted herewith as **Exhibit A**).

To counter the Examiner's contention that the claims are inherently anticipated, Applicants point to the disclosure of *Kjaergaard* that describes experiments showing that anti-OX40 antibodies do not ***necessarily and inevitably*** treat cancers and that the therapeutic efficacy of anti-OX40 antibodies (referred to as OX40 receptor mAb in *Kjaergaard*) was influenced by a number of factors including the tumor burden, the intrinsic immunogenicity of the tumor as well as the histological site of tumor growth.

In particular, Applicants submit that *Kjaergaard* describes that "[w]hereas subdermal and intracranial growth of weakly immunogenic MCA 203 and MCA 205 sarcomas and GL261 glioma were susceptible to the mAb treatment, established ***pulmonary MCA 205 metastases were refractory to the same regimen of treatment.*** Furthermore, the mAb administration had ***no impact on the growth of the poorly immunogenic B16/D5 melanoma.***" (emphasis added; Abstract, p. 5514). *Kjaergaard* concludes that the "successful treatment is mAb dose-dependent and effected by the

intrinsic immunogenicity of tumors. It is also evident that the response of a particular tumor to the treatment varies and is dependent on the histological location of tumor growth." (see, p. 5517, first full paragraph). Based on *Kjaergaard*, anti-OX40 antibodies do not, in fact, ***necessarily and inevitably*** result in the treatment of cancer.

Thus, the simple relationship between OX-40 ligand and anti-OX40 antibodies that is presumed by the Examiner from the *Gri* disclosure is contradicted by the results described in *Kjaergaard*. That is, the effect of OX-40 ligand on the treatment of cancer would *not* have allowed one of skill in the art to predict the effect of anti-OX-40 antibodies on the treatment of cancer. Thus, there is not a necessary or inevitable correlation between the activities of OX-40 ligand and anti-OX40 antibodies.

Overall, Applicants submit that *Gri* fails to teach or suggest the claimed invention, either explicitly or inherently. Accordingly, Applicants submit that *Gri* fails to anticipate the instantly claimed methods and request that the rejection under 35 U.S.C. § 102(a) be withdrawn.

35 U.S.C. §§ 102(a) and (e)
Claims 1-2, 4, 6-8, 10, 11, 19-20, 23-24 and 26

The Examiner has rejected claims 1, 2 (canceled), 4, 6-8, 10, 11, 19-20, 23-24 and 26 (withdrawn) under 35 U.S.C. §§ 102(a) and 102(e) over US Patent Publication 2003/0035790 ("*Chen*"). The Examiner states that *Chen* discloses a method for treating cancer by administering a recombinant adenovirus engineered to express GM-CSF and an anti-OX-40 antibody. The Examiner states that *Chen* discloses that GM-CSF may be expressed in mammalian cells and discuss a cancer vaccine approach, wherein cancer cells are isolated from patients, transduced in vitro, irradiated, and administered to patients. The Examiner concludes that based on the disclosure in *Chen*, one of skill in the

art would immediately envisage a method wherein the GM-CSF expressing cells are administered, along with anti-OX-40 antibodies, to treat cancer. The Examiner further states that *Chen* discloses that the methods can be applied to treating prostate cancer.

Applicants have amended claim 1 (and claims dependent therefrom) to specify that the cytokine-expressing cellular vaccine comprises proliferation-incompetent tumor cells that express GM-CSF. Applicants respectfully submit that *Chen* fails to teach or suggest each and every limitation of the amended claims.

Chen discloses compositions and methods of treating diseases such as cancer by administering one or more compounds that activate one or more cytokine receptors and one or more compounds that activate one or more costimulatory molecules expressed by activated immune cells. In particular, *Chen* discloses injecting MCA26 tumor-bearing mice intratumorally with an adenovirus expressing mGM-CSF (see, *e.g.*, Example 10). *Chen* also discloses inducing metastatic colon cancer by implanting MCA26 tumor cells into the left lobe of the liver and then subsequently injecting adenovirus expressing mGM-CSF into tumor-bearing mice (see, *e.g.*, Example 11).

In contrast, the claimed invention relates to the administration of a cytokine-expressing cellular vaccine comprising proliferation-incompetent tumor cells that express GM-CSF. *Chen* does not teach or suggest this feature of the claimed invention. Rather than using proliferation-incompetent tumor cells to express GM-CSF, *Chen* describes injecting adenovirus expressing mGM-CSF directly into tumor-bearing animals. Therefore, *Chen* fails to teach or suggest this limitation of the amended claims.

Furthermore, the claimed invention also requires the administration at least one additional cancer therapeutic agent in combination with the cytokine-expressing cellular vaccine comprising proliferation-incompetent tumor cells that express GM-CSF,

wherein the combination results in an enhanced therapeutic effect compared to monotherapy. *Chen* also does not teach or suggest this particular combination. Therefore, *Chen* fails to teach or suggest each and every limitation of the amended claims. Accordingly, applicants request that the Examiner withdraw this rejection.

35 USC §101 - Nonstatutory Double Patenting
Claims 1-2, 4, 6-8, 10, 11, 19-20, 23-24 and 26

The Examiner has provisionally rejected claims 1, 2 (canceled), 4, 6-8, 10, 11, 19-20, 23-24 and 26 (withdrawn) on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-33 of copending Application No. 10/404,662.

Applicants request that the present basis for the provisional rejection be held in abeyance until applicants are notified that claims in the instant application are otherwise allowable.

35 U.S.C. § 103(a) – Provisional rejection
Claims 1-2, 4, 6-8, 10, 11, 19-20, 23-24 and 26

The Examiner states that claims 1, 2 (canceled), 4, 6-8, 10, 11, 19-20, 23-24 and 26 (withdrawn) are directed to an invention not patentably distinct from claim 1-33 of commonly assigned Application No. 10/404,662. The Examiner states that the USPTO normally will not institute an interference between applications or a patent and an application of common ownership (citing MPEP Chapter 2300). The Examiner states that commonly assigned Application No. 10/404,662 would form the basis for a rejection of the noted claims under 35 U.S.C. § 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. The Examiner

states that in order to resolve this issue, the assignee can, under 35 U.S.C. § 103(c) and 35 C.F.R. § 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

Applicants respectfully submit that the invention of copending Application No. 10/404,662 and the present claimed invention were commonly owned by and subject to assignment to Cell Genesys, Inc. at the time the present claimed invention was made. The inventors of copending Application No. 10/404,662 (Moskalenko, Li, Aung, Prell, Creson, and Jooss) were all employed by and obligated to assign inventions to Cell Genesys, Inc. at the time the subject matter in Application No. 10/404,662 was invented. The inventors of the pending case (Moskalenko, Li, Aung, Prell, Creson, Jooss and Du) were all employed by and obligated to assign inventions to Cell Genesys, Inc. at the time the subject matter in the pending case was invented. *See* the assignment for Application No. 10/404,662 (Reel 014451, Frame 0187) (executed August 8, 2003 and August 19, 2003) **(Exhibit B)** and the assignment in the pending case (Reel 015754, Frame 0515) (executed July 1, 2004) **(Exhibit C)** (copies enclosed). Applicants also enclose copies of the *Notice of Recordation of Assignment* as received from the USPTO for Application No. 10/404,662 (**Exhibit D**, recorded September 2, 2003) and the pending case (**Exhibit E**, recorded September 2, 2004). Applicants respectfully submit that they have satisfied the requirements under 35 U.S.C. § 103(c) and 35 C.F.R. § 1.78(c) to show that the conflicting inventions were commonly owned at the time the invention in this application was made.

CONCLUSION

In view of the above, applicants request that the Examiner examine the pending claims in this application. Applicants request favorable consideration and early allowance of the pending claims.

Respectfully submitted,

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